



## Polymorphisms in NF-kappa B, PXR, LXR, PPAR gamma and risk of inflammatory bowel disease

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*Published in:*  
World Journal of Gastroenterology

*Link to article, DOI:*  
[10.3748/wjg.v17.i2.197](https://doi.org/10.3748/wjg.v17.i2.197)

*Publication date:*  
2011

*Document Version*  
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

*Citation (APA):*  
Andersen, V., Christensen, J., Ernst, A., Jacobsen, B. A., Tjonneland, A., Krarup, H. B., & Vogel, U. B. (2011). Polymorphisms in NF-kappa B, PXR, LXR, PPAR gamma and risk of inflammatory bowel disease. *World Journal of Gastroenterology*, 17(2), 197-206. <https://doi.org/10.3748/wjg.v17.i2.197>

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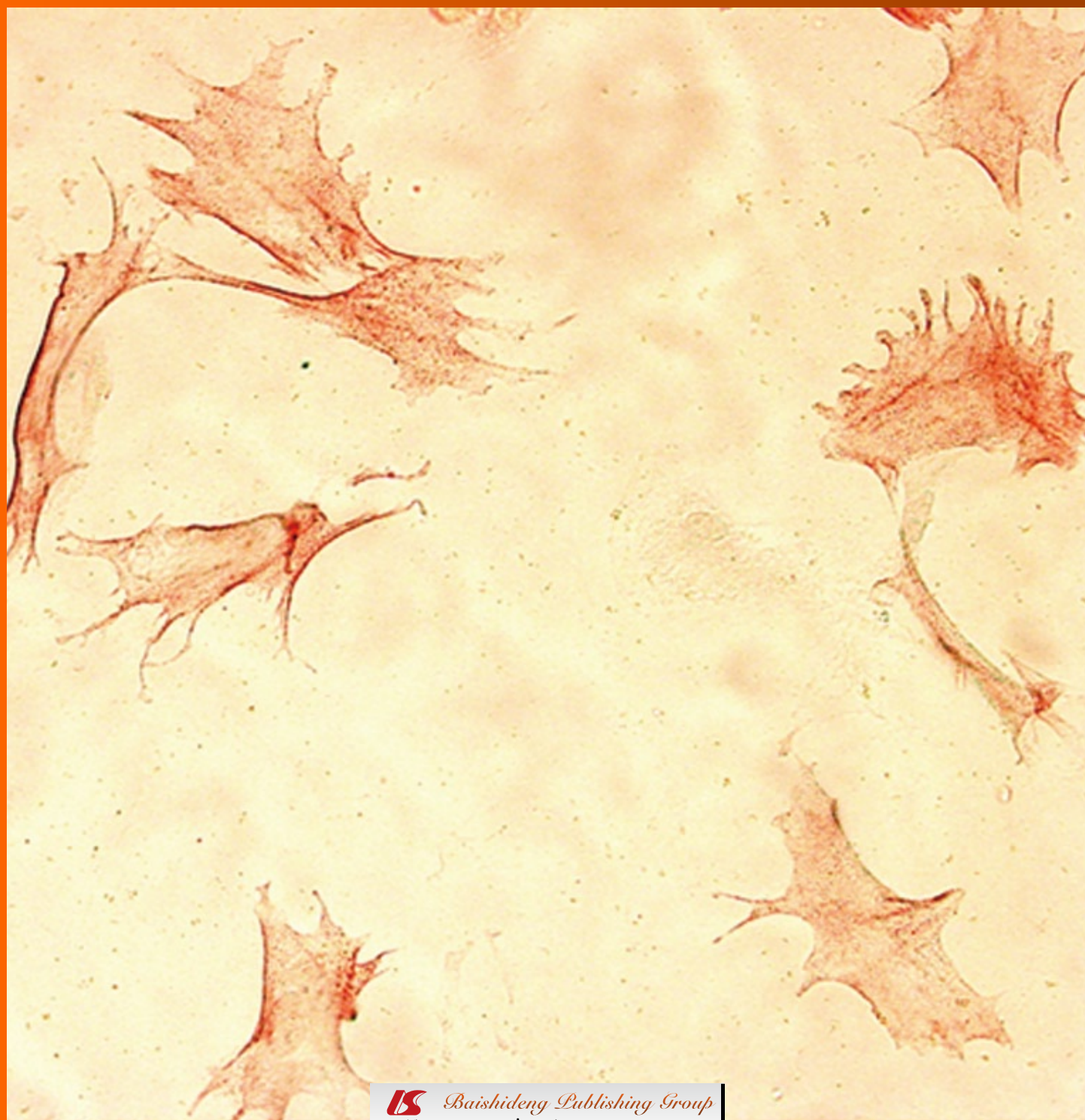
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# World Journal of *Gastroenterology*

*World J Gastroenterol* 2011 January 14; 17(2): 137-272





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*World J Gastroenterol* 2011; 17(2): 164-173  
<http://www.wjgnet.com/1007-9327/full/v17/i2/164.htm>

**AIM AND SCOPE** *World Journal of Gastroenterology* (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, DOI: 10.3748) is a weekly, open-access, peer-reviewed journal supported by an editorial board of 1144 experts in gastroenterology and hepatology from 60 countries.  
The major task of *WJG* is to report rapidly the most recent results in basic and clinical research on esophageal, gastrointestinal, liver, pancreas and biliary tract diseases, *Helicobacter pylori*, endoscopy and gastrointestinal surgery, including: gastroesophageal reflux disease, gastrointestinal bleeding, infection and tumors; gastric and duodenal disorders; intestinal inflammation, microflora and immunity; celiac disease, dyspepsia and nutrition; viral hepatitis, portal hypertension, liver fibrosis, liver cirrhosis, liver transplantation, and metabolic liver disease; molecular and cell biology; geriatric and pediatric gastroenterology; diagnosis and screening, imaging and advanced technology.

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**NAME OF JOURNAL**  
*World Journal of Gastroenterology*

**LAUNCH DATE**  
October 1, 1995

**RESPONSIBLE INSTITUTION**  
Department of Science and Technology of Shanxi Province

**SPONSOR**  
Taiyuan Research and Treatment Center for Digestive Diseases, 77 Shuangta Xijie, Taiyuan 030001, Shanxi Province, China

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**PUBLISHING**  
Baishideng Publishing Group Co., Limited, Room 1701, 17/F, Henan Building, No.90 Jaffe Road, Wanchai, Hong Kong, China  
Fax: +852-3115-8812  
Telephone: +852-5804-2046  
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Beijing Baishideng BioMed Scientific Co., Ltd., Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China  
Telephone: +86-10-8538-1892  
Fax: +86-10-8538-1893  
E-mail: [baishideng@wjgnet.com](mailto:baishideng@wjgnet.com)  
<http://www.wjgnet.com>

**PRINT SUBSCRIPTION**  
RMB 245 Yuan for each issue, RMB 11760 Yuan for one year.

**ONLINE SUBSCRIPTION**  
One-Year Price 864.00 USD

**PUBLICATION DATE**  
January 14, 2011

**CSSN**  
ISSN 1007-9327 (print)  
ISSN 2219-2840 (online)

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## Polymorphisms in NF- $\kappa$ B, PXR, LXR, PPAR $\gamma$ and risk of inflammatory bowel disease

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**Supported by** This project was supported by the "Familien Erichsen Mindefond", the Lundbeck Foundation, the Danish Research Council, the Western Danish Research Forum for Health Science, the County of Viborg, the Danish Colitis-Crohn Association, "John M Klein og hustrus mindelegat", and the A.P. Møller Foundation for the Advancement of Medical Science

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Received: May 28, 2010 Revised: August 14, 2010

Accepted: August 21, 2010

Published online: January 14, 2011

1801282) and C1431T (rs 3856806); pregnane X receptor (PXR) (NR1I2) *PXR* A-24381C (rs1523127), C8055T (2276707), and A7635G (rs 6785049); and liver X receptor (LXR) (NR1H2) *LXR* T-rs1405655-C and T-rs2695121-C were assessed in a Danish case-control study of 327 Crohn's disease patients, 495 ulcerative colitis (UC) patients, and 779 healthy controls. Odds ratio (OR) and 95% CI were estimated by logistic regression models.

**RESULTS:** The *PXR* A7635G variant, the *PPAR $\gamma$*  Pro12Ala and *LXR* T-rs2695121-C homozygous variant genotypes were associated with risk of UC (OR: 1.31, 95% CI: 1.03-1.66,  $P = 0.03$ , OR: 2.30, 95% CI: 1.04-5.08,  $P = 0.04$ , and OR: 1.41, 95% CI: 1.00-1.98,  $P = 0.05$ , respectively) compared to the corresponding homozygous wild-type genotypes. Among never smokers, *PXR* A7635G and the *LXR* T-rs1405655-C and T-rs2695121-C variant genotypes were associated with risk of IBD (OR: 1.41, 95% CI: 1.05-1.91,  $P = 0.02$ , OR: 1.63, 95% CI: 1.21-2.20,  $P = 0.001$ , and OR: 2.02, 95% CI: 1.36-2.99,  $P = 0.0005$ , respectively) compared to the respective homozygous variant genotypes. *PXR* A7635G (rs6785049) variant genotype was associated with a higher risk of UC diagnosis before the age of 40 years and with a higher risk of extensive disease (OR: 1.34, 95% CI: 1.03-1.75 and OR: 2.49, 95% CI: 1.24-5.03, respectively).

**CONCLUSION:** Common *PXR* and *LXR* polymorphisms may contribute to risk of IBD, especially among never smokers.

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### Abstract

**AIM:** To investigate the contribution of polymorphisms in nuclear receptors to risk of inflammatory bowel disease (IBD).

**METHODS:** Genotypes of nuclear factor (NF)- $\kappa$ B (NFKB1) *NF $\kappa$ B* -94ins/del (rs28362491); peroxisome proliferator-activated receptor (PPAR)- $\gamma$  (*PPAR $\gamma$* ) *PPAR $\gamma$*  Pro12Ala (rs

**Key words:** Crohn's disease; Genetic susceptibility; Single nucleotide polymorphisms; Smoking status; Transcription factors; Ulcerative colitis

**Peer reviewer:** María IT López, Professor, Experimental Biology, University of Jaen, araje de las Lagunillas s/n, Jaén 23071, Spain

Andersen V, Christensen J, Ernst A, Jacobsen BA, Tjønneland A, Krarup HB, Vogel U. Polymorphisms in NF- $\kappa$ B, PXR, LXR, PPAR $\gamma$  and risk of inflammatory bowel disease. *World J Gastroenterol* 2011; 17(2): 197-206 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v17/i2/197.htm> DOI: <http://dx.doi.org/10.3748/wjg.v17.i2.197>

## INTRODUCTION

Chronic inflammatory bowel diseases (IBDs), ulcerative colitis (UC), and Crohn's disease (CD) are complex diseases that result from the interaction of numerous genetic and environmental factors<sup>[1,2]</sup>. Recent studies have increased dramatically the number of genes known to be involved in IBD<sup>[3-7]</sup>. However, the contribution of *NOD2* gene polymorphisms to IBD etiology in populations of Northern Europe is relatively small<sup>[8-10]</sup>, which has heightened interest in resolving the genetic determinants of IBD in these countries.

The rising incidence of IBD in the West suggests that environmental factors play a major role in its pathogenesis. The intestinal lumen contains a vast array of different substances that may interact with the host, such as dietary factors, microbial components, and environmental pollutants. Many of these stimuli interact with the transcription factor nuclear factor (NF)- $\kappa$ B *via* activation of Toll-like receptors (TLRs) such as TLR4<sup>[11,12]</sup>. Nuclear receptors are intracellular transcription factors that are activated by ligands<sup>[13]</sup>, which constitute a link between environmental factors and the regulation of many cellular processes, including inflammation<sup>[14-16]</sup>. Thus, genetic variation in certain transcription factors may modify the regulation of relevant environmental factors and the associated risk of IBD.

Activation of NF- $\kappa$ B leads to the induction of pro-inflammatory signal cascades<sup>[13,17]</sup> and the resolution of intestinal inflammation<sup>[18-20]</sup>. Studies on animal models of colitis<sup>[21,22]</sup> and IBD patients<sup>[23,24]</sup> suggest that impaired NF- $\kappa$ B function leads to IBD. A polymorphism that involves deletion of four nucleotides in the NF- $\kappa$ B promoter region, named -94ATTG ins/del, has been associated with attenuated promoter activity in luciferase reporter studies<sup>[25]</sup>. The variant allele has been investigated as an IBD risk gene, but the results of these studies have been inconsistent<sup>[24-31]</sup>.

Activation of the nuclear receptors peroxisome proliferator-activated receptor (PPAR) $\gamma$ , pregnane X receptor (PXR), and liver X receptor (LXR) leads to transcriptional regulation of pro-inflammatory target genes<sup>[14,32,33]</sup> and inhibition of NF- $\kappa$ B activity<sup>[15,16,34,35]</sup>, which results in a decrease in inflammation.

Studies of animal colitis models<sup>[36-38]</sup> and IBD patients<sup>[39]</sup> have suggested that impaired PPAR $\gamma$  expression may confer IBD. The PPAR $\gamma$  Pro12Ala variant allele is in tight linkage with the PPAR $\gamma$  C1431T variant allele<sup>[40]</sup>, and the Pro to Ala substitution results in decreased transcriptional activation of target genes<sup>[41]</sup>. Studies on the associa-

tion of the PPAR $\gamma$  C1431T and Pro12Ala polymorphisms with a risk for IBD have demonstrated varying results<sup>[42-44]</sup>.

Loss of PXR function has been associated with intestinal inflammation in animal studies<sup>[15]</sup>, and low levels of PXR expression have been found in the intestine of UC patients<sup>[45]</sup>. The PXR A7635G (rs6785049) homozygous variant genotypes and PXR C8055T (rs2276707) variant genotypes have been associated with a pronounced induction of a PXR target gene, *CYP3A4*, after treatment with rifampin<sup>[46]</sup>. However, studies of PXR polymorphisms in relation to the risk for IBD have been inconsistent<sup>[47-50]</sup>.

Loss of LXR function compromised innate immunity in an animal model, which was attenuated after LXR administration<sup>[14]</sup>. The LXR tag polymorphisms in intron 7 rs1405655 and intron 2 rs2695121 have been previously investigated as candidate gene targets involved in Alzheimer's disease<sup>[51-53]</sup>.

Tobacco smoke is a source of many exogenous compounds and induces inflammation<sup>[54]</sup>. Moreover, smoking differentially affects the risk of CD and UC<sup>[55]</sup>, and the underlying mechanisms behind these effects are poorly understood<sup>[56]</sup>.

Accordingly, altered responses of NF- $\kappa$ B, PPAR $\gamma$ , PXR, and LXR to environmental pathogens may be involved in susceptibility to IBD. Hence, genetic variations in the transcription factors may modify the inflammatory response to environmental stimuli and affect the risk for IBD.

In the present study, we determined the allele and haplotype frequencies of polymorphisms in the genes that encode the transcription factors NF- $\kappa$ B (*NFKB1*) -94ins/del (rs28362491); PPAR $\gamma$  (*PPARG*) Pro12Ala (rs 1801282) and C1431T (rs 3856806); PXR (*NR1I2*) A-24381C (rs1523127), C8055T (rs2276707-T), and A7635G (rs 6785049); and LXR $\beta$  (*NR1H2*) T-rs1405655-C and T-rs2695121-C. These polymorphisms were investigated together with the smoking status in a Danish cohort of 327 patients with CD, 495 patients with UC, and 779 healthy controls.

## MATERIALS AND METHODS

### Ethics

All subjects received written and oral information and provided written informed consent. The study was performed in accordance with the Declaration of Helsinki and was approved by the local Scientific Ethical Committees (VN2003/124).

### Patients and controls

Diagnosis of CD or UC was based on clinical, radiological, endoscopic and histological examinations (infectious and other cases of IBD were excluded)<sup>[56-58]</sup>. Patients were recruited from Viborg, Aalborg, and Herning Regional Hospitals from January 2004 to March 2005. Healthy blood donors recruited from Viborg Hospital served as controls. All subjects were Caucasian and older than 18 years of age. Data on the extent of the disease (CD: L1, L2, L3, UC: E1, E2, E3), family history, surgical treatment, advanced



medical treatment, age at diagnosis (under or over 40 years of age), and information on smoking habits at the time of diagnosis (patients) and at study entry (healthy controls) were collected.

### Genotyping

Functional single nucleotide polymorphisms (SNPs) were selected based on the literature, except in the case of LXR with tag SNPs selected based on previous disease association<sup>[51-53]</sup> because there were no available data on the functional effects. DNA was extracted from EDTA-stabilized peripheral blood samples from all patients and healthy controls using either a PureGene (Gentra Systems, Minneapolis, MN, USA) or Wizard Genomic (Promega, Madison, WI, USA) DNA purification kit, according to the manufacturers' recommendations.

Genotypes were determined by Taqman allelic discrimination (ABI 7500/7900HT, Applied Biosystems). DNA (20 ng) was analyzed in volumes of 4  $\mu$ L. Samples from cases and sub-cohort members were mixed during genotyping, and laboratory staff were blinded to the case or control status during analysis. Known genotype controls were included in each run. To confirm reproducibility, 10% of the samples were genotyped again. The genotypes exhibited 100 % identity.

NF $\kappa$ B (NFKB1) ATTG ins/del (rs28362491) and PPAR $\gamma$  (PPARG) Pro12Ala were genotyped as previously described<sup>[59]</sup> and<sup>[60]</sup>, respectively). PPAR $\gamma$  (PPARG) C1431T<sup>[61]</sup>, PXR (NR1I2) A-24381C (rs1523127), C8055T (rs2276707), and A7635G (rs6785049); and LXR- $\beta$  (NR1H2) T-rs1405655C and T-rs2695121C were assessed using developed assays (Applied Biosystems).

### Statistical analysis

Logistic regression was utilized to analyze the relationship between the investigated polymorphisms and IBD. The statistical analysis included only subjects with all necessary information available. Age was entered linearly in the model after verifying these data using a linear spline<sup>[62]</sup>. Subgroup analyses were performed on polymorphisms in relation to the extent of the disease (CD: L1, L2, L3, UC: E1, E2, E3), family history, surgical treatment, advanced medical treatment, and age at diagnosis (above or below 40 years of age) for all cases. The haplotypes were inferred manually as described previously<sup>[63]</sup>.

### Power analysis

The Genetic Power Calculator for case-control was utilized for power analysis of discrete traits<sup>[64]</sup>. This study had greater than 80% power to detect a dominant effect with an odds ratio (OR) of 1.5 in either CD or UC, or 1.4 if CD and UC were combined.

## RESULTS

### Study population description

Characteristics of the Danish IBD patients and controls are shown in Table 1. Current smoking was more common among CD than UC patients, with incidences of

Table 1 Description of study participants *n* (%)

	CD ( <i>n</i> = 327)	UC ( <i>n</i> = 495)	Controls ( <i>n</i> = 779)
Sex			
Male	129 (39)	239 (48)	400 (51)
Female	198 (61)	256 (51)	379 (49)
Age (yr)			
Median (5%-95%)	43 (23-76)	49 (24-76)	43 (23-60)
Age at diagnosis (yr)			
Median (5%-95%)	30 (15-64)	35 (17-68)	
Smoking habits			
Smokers	167 (51)	86 (17)	205 (26)
Never smokers	115 (35)	226 (46)	391 (50)
Former smokers	45 (14)	183 (37)	183 (23)
Location of UC			
Proctitis (E1)		207 (42)	
Left side (E2)		183 (37)	
Extensive (E3)		93 (19)	
Data not available		12 (2)	
Location of CD			
Colonic (L2)	151 (46)		
Ileal (L1)	74 (23)		
Ileocolonic (L3)	89 (27)		
Data not available	13 (4)		
Medication			
Advanced <sup>1</sup>	140 (43)	103 (21)	
No advanced medication <sup>2</sup>	182 (56)	389 (79)	
Data not available	5 (2)	3 (1)	
Operation			
Yes	149 (46)	14 (3)	
No	171 (52)	472 (95)	
Data not available	7 (2)	9 (2)	

Disease location was classified according to the WGO Montreal classification. Statistical analyses included subjects for whom all information was available. <sup>1</sup>Azathioprine, 6-mercaptopurine, tumor necrosis factor inhibitors, or methotrexate; <sup>2</sup>5-aminosalicylic acid, prednisolone. CD: Crohn's disease; UC: Ulcerative colitis.

51% and 17%, respectively. The genotype distributions among the controls did not deviate from Hardy-Weinberg equilibrium. The variant allele frequencies of the studied polymorphisms are shown in Table 2.

### Associations between polymorphisms and disease phenotypes

The association between genotypes and the disease risk was analyzed separately for CD and UC (Table 3). The PXR A7635G (rs6785049) variant genotypes, PPAR $\gamma$  Pro12Ala homozygous variant, and LXR T-rs2695121-C homozygous genotypes were associated with a higher risk of UC, as compared to the homozygous wild-type genotype (OR: 1.31, 95% CI: 1.03-1.66, *P* = 0.03, OR: 2.30, 95% CI: 1.04-5.08, *P* = 0.04, and OR: 2.41, 95% CI: 1.00-1.98, *P* = 0.05, respectively). No association was found between risk of CD and any genotype. Furthermore, no association was found between NF $\kappa$ B -94 ins/del or PPAR $\gamma$  C1431T polymorphisms and disease risk (Table 3).

### Interaction between gene polymorphisms and smoking

The association between genotypes and disease risk was analyzed for current smokers, previous smokers, and never smokers. There was no interaction between smoking

**Table 2** Allele frequencies for the gene polymorphisms in Crohn's disease and ulcerative colitis patients *n* (%)

	CD	UC	Controls
NF- $\kappa$ B -94ins/del			
I	379 (58)	583 (59)	919 (59)
D	275 (42)	407 (41)	639 (41)
PPAR $\gamma$ Pro <sup>12</sup> Ala			
C	564 (86)	844 (85)	1315 (84)
G	90 (14)	146 (15)	243 (16)
PPAR $\gamma$ C1431T			
C	560 (86)	832 (84)	1327 (85)
T	94 (14)	158 (16)	231 (15)
PXR rs1523127			
A	395 (60)	570 (58)	926 (59)
C	259 (40)	420 (42)	632 (41)
PXR rs2276707			
C	540 (83)	825 (83)	1275 (82)
T	114 (17)	165 (17)	283 (18)
PXR rs6785049			
A	426 (65)	615 (62)	1011 (65)
G	228 (35)	375 (38)	547 (35)
LXR rs1405655			
T	435 (67)	675 (68)	1079 (69)
C	219 (33)	315 (32)	479 (31)
LXR rs2695121			
T	292 (45)	430 (43)	727 (47)
C	362 (55)	560 (57)	831 (53)

NF- $\kappa$ B: Nuclear factor  $\kappa$ B; PPAR $\gamma$ : Peroxisome proliferator-activated receptor  $\gamma$ ; CD: Crohn's disease; UC: Ulcerative colitis; PXR: Pregnane X receptor; LXR: Liver X receptor.

status and gene polymorphisms in relation to the risk of CD or UC (data not shown). In general, there was an association between smoking status and the risk of CD and UC. The OR for risk of CD was high among smokers and low among former smokers, regardless of genotype status. In contrast, the OR for UC was high among former smokers and low among current smokers, regardless of genotype.

The ORs for associations between genotypes and the risk of CD, UC and combined IBD among individuals that had never smoked are shown in Table 4. The ORs were analyzed separately for CD and UC and for the combined groups to describe the risk of IBD because there was no heterogeneity between the two groups. The PXR A7635G (rs6785049) and LXR T-rs1405655-C and T-rs2695121-C variant genotypes were associated with a higher risk for IBD, as compared to the homozygous wild-type genotypes (OR: 1.41, 95% CI: 1.05-1.91,  $P = 0.02$  and OR: 1.63, 95% CI: 1.21-2.20,  $P = 0.001$ , OR: 2.02, 95% CI: 1.36-2.99,  $P = 0.0005$ , respectively).

### Haplotype analysis

Haplotype analysis among the healthy controls demonstrated that the PXR C8055T variant genotype was more frequent in carriers of the PXR A7635G variant allele than among carriers of the A7635G wild-type, which indicated that these two polymorphisms were linked. Moreover, the presence of the A-24381C variant allele seemed to be independent of the PXR C8055T and A7635G genotypes. No significant association of PXR haplotypes and disease risk

was determined (data not shown). Tables 5 and 6 show the minor allele frequencies of the PXR polymorphisms compared to those in other studies, and published associations between PXR polymorphisms and risk of IBD<sup>[47-59]</sup>.

Haplotype analysis in the healthy controls demonstrated that carriage of the LXR rs1405655 C variant allele was linked to the presence of the LXR rs2695121 C variant allele. Carriage of the LXR rs1405655 C allele in this instance did not add to the risk of IBD, compared to carriage of only the rs2695121 C allele. The OR for the association between the LXR haplotype that encompassed the T-rs2695121-C and the T-rs1405655-C variant allele was 1.17, 95% CI: 1.00-1.36 and 1.23, 95% CI: 1.00-1.52, compared to the compound wild-type haplotype, respectively (data not shown).

Haplotype analysis was not performed for the closely linked PPAR $\gamma$  Pro12Ala and C1431T polymorphisms.

### Subgroup analysis

Subgroup analysis revealed that the PXR A7635G (rs6785049) variant genotype was associated with a higher risk of UC diagnosis before the age of 40 years and with a higher risk of extensive disease (OR: 1.34, 95% CI: 1.03-1.75 and OR: 2.49, 95% CI: 1.24-5.03, respectively), and the LXR T-rs2695121-C variant genotype was associated with a higher risk of advanced medical treatment for UC (OR: 1.80, 95% CI: 1.08-2.99) as compared to the homozygous wild-type genotype (data not shown).

## DISCUSSION

In the present case-control study of 822 IBD patients (327 CD and 495 UC) and 773 healthy controls, we determined that PXR and LXR variant allele carriers were at higher risk of UC than the homozygous wild-type carriers, and that the association was strongest among individuals that had never smoked and those with severe UC. An association between PPAR $\gamma$  Pro12Ala and the risk of UC was determined based on only a few subjects. No associations were determined between gene polymorphisms and risk for CD or UC among previous or current smokers. Furthermore, no associations were found between the NF- $\kappa$ B gene polymorphism and risk of CD or UC. The association between LXR C-rs1405655-T and T-rs2695121-C variant genotypes and the risk of IBD among individuals that had never smoked withstood Bonferroni correction for multiple testing, whereas the other associations were not validated by these analyses. The strengths and weaknesses of the present study must be considered<sup>[65]</sup>. For instance, one strength of the present study is the well-characterized study subjects with information that included smoking status. There are various methods used to determine the control group with associated advantages and disadvantages<sup>[66]</sup>. In this study, the control group consisted of blood donors, who were not a random sample of the population. However, confounding data is not a likely explanation of the association because both cases and controls were not aware of their genotypes, and geno-

**Table 3** Odds ratio for the studied gene polymorphisms in Crohn's disease and ulcerative colitis patients

	CD	UC	Control	OR <sub>CD</sub>	95% CI <sup>1</sup>	P value	OR <sub>UC</sub>	95% CI <sup>1</sup>	P value
NF- $\kappa$ B -94ins/del									
II	107	175	267	1.00	-		1.00	-	
ID	165	233	385	1.08	0.80-1.46	0.62	0.94	0.72-1.21	0.62
DD	55	87	127	1.21	0.81-1.81	0.36	1.04	0.73-1.47	0.83
ID and DD	220	320	512	1.11	0.83-1.48	0.48	0.96	0.75-1.23	0.76
PPAR $\gamma$ Pro <sup>12</sup> Ala									
CC	240	364	549	1.00	-		1.00	-	
CG	84	116	217	0.88	0.65-1.20	0.43	0.83	0.63-1.09	0.17
GG	3	15	13	0.48	0.13-1.77	0.27	2.30	1.04-5.08	0.04
CG and GG	87	131	230	0.86	0.64-1.16	0.33	0.90	0.69-1.17	0.42
PPAR $\gamma$ C1431T									
CC	241	352	561	1.00	-		1.00	-	
CT	78	128	205	0.81	0.59-1.12	0.20	1.00	0.76-1.31	0.99
TT	8	15	13	1.36	0.54-3.42	0.52	1.95	0.90-4.27	0.09
CT and TT	86	143	218	0.85	0.62-1.15	0.29	1.05	0.81-1.37	0.69
PXR rs1523127									
AA	114	160	280	1.00	-		1.00	-	
AC	167	250	366	1.06	0.79-1.43	0.71	1.15	0.89-1.50	0.29
CC	46	85	133	0.89	0.59-1.35	0.59	1.11	0.78-1.56	0.57
AC and CC	213	335	499	1.02	0.77-1.35	0.91	1.14	0.89-1.46	0.30
PXR rs2276707									
CC	223	339	517	1.00	-		1.00	-	
CT	94	147	241	0.92	0.68-1.24	0.57	0.97	0.75-1.26	0.84
TT	10	9	21	1.25	0.56-2.76	0.58	0.67	0.30-1.51	0.33
CT and TT	104	156	262	0.94	0.71-1.26	0.69	0.95	0.74-1.22	0.68
PXR rs6785049									
AA	137	184	334	1.00	-		1.00	-	
AG	152	247	343	1.12	0.84-1.49	0.46	1.35	1.05-1.74	0.02
GG	38	64	102	0.91	0.58-1.40	0.66	1.18	0.81-1.71	0.39
AG and GG	190	311	445	1.07	0.81-1.40	0.65	1.31	1.03-1.66	0.03
LXR rs1405655									
TT	143	229	383	1.00	-		1.00	-	
CT	149	217	313	1.26	0.95-1.68	0.11	1.22	0.95-1.57	0.11
CC	35	49	83	1.12	0.71-1.78	0.62	1.01	0.67-1.51	0.97
CT and CC	184	266	396	1.23	0.94-1.62	0.13	1.18	0.93-1.49	0.17
LXR rs2695121									
TT	62	88	170	1.00	-		1.00	-	
CT	168	254	387	1.28	0.90-1.83	0.17	1.30	0.95-1.77	0.10
CC	97	153	222	1.21	0.82-1.79	0.34	1.41	1.00-1.98	0.05
CT and CC	265	407	609	1.26	0.89-1.76	0.19	1.34	0.99-1.79	0.06

Statistical analyses included subjects for whom all information was available. <sup>1</sup>Adjusted for age, sex and smoking status. NF- $\kappa$ B: Nuclear factor  $\kappa$ B; PPAR $\gamma$ : Peroxisome proliferator-activated receptor  $\gamma$ ; CD: Crohn's disease; UC: Ulcerative colitis; OR: Odds ratio; PXR: Pregnane X receptor; LXR: Liver X receptor.

typing was performed blindly. Furthermore, stratification could theoretically result in the determined associations. However, this possibility is considered unlikely because the cohort was recruited from an area of Denmark with a homogeneous population<sup>[67]</sup>. Minor allele frequencies of *PXR* polymorphisms in the present study and in other published studies on Caucasian populations are shown in Table 5. The allele frequencies of the present study did not deviate from previously determined frequencies<sup>[47,49,50]</sup>. Therefore, heterogeneity or stratification in the control group is not a likely explanation for the determined associations in our study (Table 5).

The present study included 1600 participants, and power analysis determined that this study had more than 80% power to detect a dominant effect with an OR of 1.5 in relation to either CD or UC, and 1.4 when CD and UC were combined. Moreover, genetic determinants may be stronger among patients with extensive development of

the disease<sup>[68,69]</sup> and disease onset at a younger age. However, the obtained results cannot be excluded as false positive.

An association of the *NF- $\kappa$ B* -94 ins/del with UC, CD, or IBD was not determined in the present study. The variant allele has been associated with a risk of UC in a study that used the family-based association test and the transmission disequilibrium test in 131 IBD pedigrees with UC offspring, which was replicated in a second set of 258 UC and 653 healthy controls with an OR for the combined studies of 1.57 (1.14-2.16)<sup>[25]</sup>. This study was further replicated in a small study of 127 UC patients and 155 healthy controls<sup>[26]</sup>, whereas larger studies have not indicated any association between the polymorphism and IBD<sup>[27-29]</sup>, UC<sup>[30,31]</sup>, or CD<sup>[24]</sup>. Our results are in accordance with the latter studies<sup>[27-31]</sup>.

In the present study, a statistically significant (although modest) association was determined between the homozygous *PPAR $\gamma$*  Pro12Ala variant genotype and an increased



**Table 4** Odds ratio for the gene polymorphisms among Crohn's disease and ulcerative colitis never smokers

	NS-CD	NS-UC	NS-control	OR <sub>NS-CD</sub>	95% CI <sup>1</sup>	P value	OR <sub>NS-UC</sub>	95% CI <sup>1</sup>	P value	OR <sub>NS-IBD</sub>	95% CI <sup>1</sup>	P value
NF-κB -94ins/del												
II	40	79	136	1.00	-		1.00	-		1.00	-	
ID	56	109	194	0.99	0.62-1.57	0.97	0.98	0.68-1.42	0.93	0.98	0.71-1.36	0.92
DD	19	38	61	1.07	0.57-2.00	0.83	1.09	0.67-1.79	0.72	1.09	0.70-1.68	0.71
ID and DD	75	147	255	1.01	0.65-1.56	0.97	1.01	0.72-1.43	0.95	1.01	0.74-1.37	0.96
PPAR $\gamma$ Pro <sup>12</sup> Ala												
CC	83	167	270	1.00	-		1.00	-		1.00	-	
CG	31	50	117	0.86	0.54-1.38	0.54	0.71	0.48-1.04	0.08	0.75	0.54-1.05	0.09
GG	1	9	4	0.80	0.09-7.29	0.84	3.99	1.20-13.32	0.02	2.77	0.85-9.00	0.09
CG and GG	32	59	121	0.86	0.54-1.37	0.53	0.81	0.56-1.17	0.26	0.82	0.59-1.13	0.21
PPAR $\gamma$ C1431T												
CC	85	163	285	1.00	-		1.00	-		1.00	-	
CT	26	56	100	0.88	0.53-1.44	0.60	0.98	0.67-1.44	0.93	0.93	0.67-1.31	0.70
TT	4	7	6	2.16	0.59-7.90	0.24	2.05	0.67-6.26	0.21	2.06	0.75-5.67	0.16
CT and TT	30	63	106	0.95	0.59-1.53	0.83	1.04	0.72-1.51	0.82	1.00	0.72-1.39	0.99
PXR rs1523127												
AA	43	74	149	1.00	-		1.00	-		1.00	-	
AC	51	103	176	1.01	0.64-1.60	0.97	1.15	0.79-1.67	0.46	1.11	0.80-1.53	0.54
CC	21	49	66	1.10	0.60-1.99	0.77	1.52	0.95-2.41	0.08	1.36	0.90-2.05	0.15
AC and CC	72	152	242	1.03	0.67-1.59	0.89	1.25	0.88-1.77	0.21	1.17	0.87-1.59	0.30
PXR rs2276707												
CC	73	150	260	1.00	-		1.00	-		1.00	-	
CT	36	70	119	1.08	0.69-1.70	0.74	1.03	0.72-1.47	0.89	1.04	0.76-1.43	0.81
TT	6	6	12	1.76	0.64-4.86	0.27	0.86	0.31-2.34	0.76	1.16	0.51-2.63	0.73
CT and TT	42	76	131	1.14	0.74-1.76	0.55	1.01	0.71-1.43	0.96	1.05	0.77-1.43	0.75
PXR rs6785049												
AA	42	77	168	1.00	-		1.00	-		1.00	-	
AG	52	119	176	1.19	0.75-1.88	0.47	1.49	1.04-2.13	0.03	1.38	1.01-1.89	0.05
GG	21	30	47	1.79	0.97-3.31	0.06	1.40	0.82-2.39	0.22	1.53	0.97-2.43	0.07
AG and GG	73	149	223	1.31	0.85-2.02	0.21	1.47	1.04-2.07	0.03	1.41	1.05-1.91	0.02
LXR rs1405655												
TT	43	95	203	1.00	-		1.00	-		1.00	-	
CT	55	106	154	1.69	1.07-2.65	0.02	1.54	1.08-2.18	0.02	1.58	1.16-2.16	0.004
CC	17	25	34	2.32	1.19-4.55	0.01	1.66	0.93-2.95	0.09	1.85	1.12-3.07	0.02
CT and CC	72	131	188	1.80	1.18-2.77	0.01	1.56	1.11-2.17	0.01	1.63	1.21-2.20	0.001
LXR rs2695121												
TT	15	30	90	1.00	-		1.00	-		1.00	-	
CT	59	126	197	1.82	0.98-3.39	0.06	1.98	1.23-3.17	0.005	1.93	1.28-2.92	0.002
CC	41	70	104	2.37	1.23-4.57	0.01	2.09	1.25-3.49	0.005	2.18	1.39-3.41	0.0007
CT and CC	100	196	301	2.01	1.11-3.64	0.02	2.01	1.28-3.17	0.002	2.02	1.36-2.99	0.0005

Statistical analyses included subjects for whom all information was available. <sup>1</sup>Adjusted for age and sex. NS: Never smoker; NF-κB: Nuclear factor κB; PPAR $\gamma$ : Peroxisome proliferator-activated receptor  $\gamma$ ; CD: Crohn's disease; UC: Ulcerative colitis; OR: Odds ratio; PXR: Pregnane X receptor; LXR: Liver X receptor.

**Table 5** Minor allele frequencies of pregnane X receptor polymorphisms in studied populations

	Controls	C-rs3814055-T	A-rs1523127-C	C-rs2276707-T	A-rs6785049-G	
Danish	779		0.41	0.18	0.35	Present study
Irish	336	0.433	0.452	0.142	0.406	Dring <i>et al</i> <sup>[47]</sup>
Scottish	334		0.394			Ho <i>et al</i> <sup>[49]</sup>
Spanish	550	0.382		0.192		Martínez <i>et al</i> <sup>[50]</sup>

Rs3814055 and rs1523127 are closely linked.

risk of IBD. This result cannot be excluded as random because of the small sample size. In a combined Dutch and Chinese study, the PPAR $\gamma$  C1431T variant allele was associated with UC in the Chinese study group but not in the Dutch study group, and no associations were indicated with CD<sup>[42]</sup>. No associations between PPAR $\gamma$  Pro12Ala polymorphism and UC<sup>[43]</sup> or CD<sup>[44]</sup> have been demonstrated in two small studies. Therefore, these collective studies

have not yielded consistent data that supported involvement of PPAR $\gamma$  in IBD.

PXR A7635G (rs6785049) variant allele carriers were at a higher risk of UC and IBD than homozygous wild-type carriers were. Furthermore, risk was highest among individuals that had never smoked. Table 6 shows the results of published association studies of PXR polymorphisms in IBD. The risk allele is indicated for positive

**Table 6** Published associations between pregnane X receptor polymorphisms and inflammatory bowel disease risk

	Cases	Controls	C-25385T (rs3814055)	A-24381C (rs1523127)	C8055T (rs2276707)	A7635G (rs6785049)	
Danish <sup>1</sup>	822	779		Neg	Neg	Variant	Present study
Irish <sup>2</sup>	422	336	Wild-type	Wild-type	Variant	Wild-type	Dring <i>et al</i> <sup>[47]</sup>
Scottish <sup>2</sup>	715	334		Neg			Ho <i>et al</i> <sup>[49]</sup>
Spanish <sup>2</sup>	696	550	Variant		Wild-type		Martínez <i>et al</i> <sup>[50]</sup>
Canadian <sup>3</sup>	270	336		Neg		Neg	Amre <i>et al</i> <sup>[48]</sup>

No association is indicated by “neg”. The risk allele is indicated for positive associations between the pregnane X receptor polymorphisms and inflammatory bowel disease risk. <sup>1</sup>Associations adjusted for smoking status; <sup>2</sup>Associations not adjusted for smoking status; <sup>3</sup>Children with Crohn’s disease.

associations, whereas a null result is indicated as “neg” in Table 6. These results were inconsistent. No association was determined between the PXR A-24381C (rs1523127) polymorphism and IBD in the present study or in a previous Scottish study<sup>[49]</sup>. In contrast, Irish and Spanish studies have indicated opposite associations between IBD and the closely linked PXR C-25385T (rs3814055) polymorphism<sup>[47,50]</sup>. Furthermore, the A7635G (rs6785049) variant genotype was found to be associated with risk for UC in the present study, whereas this allele was indicated to be protective for IBD in the Irish study<sup>[47]</sup>. Collectively, these results suggest that variable linkage disequilibrium between the investigated and biologically functional SNPs, and population heterogeneity may contribute to the inconsistent results.

Low levels of PXR were expressed in the intestine of UC patients, and high PXR activity ameliorated colitis in an animal IBD model<sup>[70]</sup>. Thus, impaired PXR function may fail to suppress NF- $\kappa$ B-induced intestinal inflammation<sup>[13,71]</sup>. Moreover, attenuated activation of PXR target genes, such as the xenobiotic transporters *MDR1* (ABCB1) and *MRP2* (ABCC2), may lead to a less proficient epithelial barrier. Several lines of evidence support the role of impaired xenobiotic transport in IBD, including the development of colitis in *mdr1a*-deficient mice<sup>[72]</sup>, low *MDR1* expression levels in UC patients<sup>[73]</sup>, and a meta-analysis that indicated an association between an *MDR1* (ABCB1) polymorphism and the risk of UC<sup>[74]</sup>. Therefore, impaired PXR function may lead to less effective induction of *MDR1* and export of harmful substances that originate from bacteria, diet, and pollutants.

The present investigation yielded strong associations between the LXR T-rs2695121-C homozygous variant allele and the risk of UC, and between both of the studied LXR variants and the risk of IBD among individuals that had never smoked. Haplotype analysis suggested a strong linkage between the two polymorphisms, and that carriage of the LXR T-rs1405655-C variant genotype coupled to the other LXR polymorphism does not add to the risk of IBD, compared to carriage of only the LXR T-rs2695121-C variant genotype. These polymorphisms have only been previously investigated in relation to Alzheimer’s disease<sup>[53]</sup>. LXR seems to have anti-inflammatory properties, and LXR represses a set of inflammatory genes after activation by bacterial components or cytokines<sup>[32]</sup>. Furthermore, LXR has been recently demon-

strated to upregulate xenobiotic transport proteins, such as *MDR1* (ABCB1)<sup>[75]</sup> and *MRP2* (ABCC2)<sup>[76]</sup>. Therefore, our results suggest the involvement of LXR in UC etiology.

Finally, the present study suggested that the associations between the PXR A7635G (rs6785049) and both of the studied LXR variant genotypes and UC were stronger among never smokers than among previous or current smokers. Therefore, the impact of the PXR and LXR gene polymorphisms on population disease risk may be larger in population with low frequencies of smokers than in those with many smokers. None of the associations indicated in the previously mentioned studies were adjusted for smoking status. Therefore, differences in relevant exposure may have contributed to the inconsistent results. We have previously found that inclusion of smoking status may be essential for evaluation of genetic predisposition to IBD (unpublished data, V. Andersen), and the present study is in accordance with our former study. Moreover, recently, passive smoking has been suggested to confer risk of IBD in children<sup>[77,78]</sup>.

Tobacco smoke contains > 3000 different chemical substances that have an impact on many biological pathways in relation to IBD<sup>[55]</sup>. However, no interaction between smoking status and the studied polymorphisms was determined in the present study. Tobacco smoke suppresses NF- $\kappa$ B activation in blood mononuclear cells<sup>[58]</sup>, and a similar mechanism may occur in the intestine.

In summary, the present study of 1600 individuals suggests that PXR and LXR are implicated in determining individual susceptibility to UC in the Danish high-incidence population. Furthermore, the conferred risk seems to be strongest among individuals that have never smoked. Clearly, further research is necessary to assess the overall role of inborn variants in PXR and LXR on UC susceptibility and the underlying biological mechanisms in relation to IBD etiology. Our results suggest that inclusion of smoking status may be essential for the evaluation of the role of genetic predisposition to IBD.

## COMMENTS

### Background

Environmental and genetic factors are involved in the etiology of the chronic inflammatory bowel diseases (IBDs), ulcerative colitis (UC), and Crohn’s disease. Furthermore, gene-environment interactions may result from variants in genes involved in the handling of environmental factors.

## Research frontiers

The rising incidence of IBD in the West suggests that environmental factors play a major role in its pathogenesis. Nuclear receptors are intracellular transcription factors that constitute a link between environmental factors and the regulation of many cellular processes, including inflammation. In this study, the authors demonstrated that genetic variants in the nuclear receptors pregnane X receptor (PXR) and liver X receptor (LXR) may confer risk of UC. Furthermore, the conferred risk seems to be strongest among individuals that have never smoked.

## Innovations and breakthroughs

Recent reports have highlighted the importance of genetic variations in the etiology in IBD. This study explores the contribution of genetic variations in nuclear factors to risk of IBD. This is the first study to suggest that LXR may confer risk of UC, and moreover, add to our knowledge of risk of UC associated with PXR variants. Next, this study substantiated the authors' previous findings that inclusion of smoking status may be essential for the evaluation of the role of genetic predisposition to IBDs.

## Applications

By understanding the genetic contribution to risk of IBDs, this study adds further to our knowledge about the biological pathways that lead to disease, which is considered a prerequisite for development of new molecular targets for treatment.

## Terminology

PXR, LXR and peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) are nuclear receptors, i.e. sensors of the environment, because they are activated by the binding of various compounds termed ligands, and next, in similarity with nuclear factor (NF)- $\kappa$ B, they are transcription factors, i.e. they regulate transcription of their target genes. Thereby, nuclear factors may constitute a link between environmental factors and the regulation of inflammation.

## Peer review

The authors examined the contribution of genetic variants in the nuclear receptors PXR, LXR and PPAR $\gamma$  and the transcription factor NF- $\kappa$ B to the risk of IBDs. The study revealed that variants in genes that coded for PXR and LXR confer risk of UC, especially among never smokers. Furthermore, the study demonstrates that inclusion of smoking status may be essential for the evaluation of the role of genetic predisposition to IBDs.

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